UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

In re NATIONAL HOCKEY LEAGUE PLAYERS' CONCUSSION INJURY LITIGATION This Document Relates To: ALL ACTIONS	MDL No. 14-2551 (SRN/JSM) **REBUTTAL DECLARATION OF R. DAWN COMSTOCK, PH.D**

I. INTRODUCTION

I have reviewed the declarations submitted in this litigation by Dr. John David Cassidy ("Cassidy") (Dkt. 732-2), Dr. Christopher Randolph ("Randolph) (Dkt. 732-11, and Dr. Lisa Brenner ("Brenner") (Dkt. 732-1), particularly the sections in those declarations that address my work in this case. I have also reviewed the NHL's motion to exclude my testimony from this litigation. I offer this Rebuttal Report to address those various critiques.

II. DISCUSSION

A. Point by Point Response to Declaration of John David Cassidy

1. *Responses to Cassidy's Section III. Summary of Opinions*

a. <u>One can assert an "increased risk" without precisely measuring background risk or calculating risk ratios</u>

Cassidy opines that one cannot assert an increased risk of long term neurological disorders (LTND's) from concussions without strictly measuring the risk of LTNDs, including the background risk and risk ratios. (Cassidy ¶ 21) This, however, is an inaccurate and unnecessarily narrow view of assertion of risk. Risk ratios (RR), which are also called rate ratios, demonstrate the relative risk of an outcome of interest in one population group (often referred to as the exposed group) compared to another (often referred to as the referent group) and are interpreted as the increase in risk associated with the exposure. This metric is calculated by dividing the rate of the outcome of interest in the exposed group by the rate of the outcome of interest in the referent group.

Attributable risks (AR) demonstrate the difference between the risk in the exposed group and the referent group and are interpreted as the risk attributed to the exposure. This metric is calculated by subtracting the rate of the outcome of interest in the referent group from the rate of the outcome of interest in the exposed group. Simply stated these two metrics each provide different insights into the association between an exposure and outcome of interest. The peer-review literature clearly demonstrates that Cassidy's assertion that it is a "matter of scientific methodology" that the only appropriate way to measure risk is to calculate the AR is incorrect. Large numbers of peer-review papers exist across numerous areas of medicine which assess risk utilizing RRs. It is simply not necessary to calculate ARs in order to "assert an increased risk." In fact numerous RCTs and prospective/longitudinal cohort studies (the very studies Cassidy claims are required to definitively prove causal associations) report RRs rather than ARs, even when making causal conclusions.

Cassidy also states there are currently no studies of the risk of CTE in any comparative population or studies that measure the relative risk of CTE in athletes. (Cassidy ¶ 21). This statement is also untrue. The large 2015 brain bank study (K.F. Bieniek *et al*., Chronic traumatic encephalopathy pathology in a neurodegerative disorders brain bank, 130 ACTA NEUROPATHOL. 6, 877-89 (2015)) clearly showed increased prevalence of CTE in contact sports athletes, including ice hockey players. Thus to say there are no studies of the risk of CTE is simply disingenuous, unless of course Dr. Cassidy meant to say there are no

studies that meet his vary narrow definition of a study (e.g., a RCT or prospective/longitudinal study from which ARs were calculated).

Also, it is not impossible to scientifically assert an increased risk in the absence of RCTs or prospective/longitudinal studies. It may be impossible to definitively demonstrate *causal association*, but risk may be *asserted* through modeling studies (similar to those conducted by Dr. Cassidy), through extrapolation from studies of similar populations, through preponderance of evidence from review of case-control and cohort studies, etc.

Cassidy also opines that any assertion of increased risk of LTND that does not specifically measure the risk is merely speculation. (Cassidy ¶ 22). Again, Cassidy is simply being too restrictive in his determination. As noted above, his assertion that it is a "matter of scientific methodology" that the only appropriate way to measure risk is to calculate the AR is incorrect. Additionally, his claim that assertions of increase risk are not based on established epidemiological principles is also not widely held. For example, Hill's criteria for causation (discussed in greater detail below) allow for a preponderance of the evidence to guide public health and clinical decision making reflecting evaluation of risk in population subgroups when definitive prospective longitudinal studies have not yet been conducted – this is a valued and long held epidemiologic principle.

b. <u>One can infer causation and assert an increased risk based upon case studies</u>

Cassidy's overly restrictive statement that case studies and cross-sectional studies cannot be used to even infer causality is not, in fact, "a matter of established scientific methodology" and his claim that it does not matter if such studies are peer-reviewed or how many of such studies there are is patently false. (Cassidy ¶ 24) This statement violates several of the tenets of Hill's Criteria. It is widely accepted that a preponderance of evidence, even if that evidence is based on studies of lower methodological strength, can be utilized to demonstrate associations and to infer causality, at least until such time as those conclusions are either confirmed or refuted by studies of higher methodological strength. For example, it is simply impossible for Cassidy to claim that no epidemiologist would even infer causality after reading the recent paper by Mez et al (Mez et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA. 2017;318(4):360-370). This case series study: 1) follows numerous other case series studies published to date, each of which came to the same conclusion that CTE appears to be related to participation in football, 2) includes an incredibly large number of cases with 202 brains of football players evaluated and 177 demonstrating CTE, and 3) it demonstrates an incredibly high prevalence of CTE (99%) in the NFL players' brains evaluated. Frankly, it is irresponsible to claim that such a strong case series study should simply be discounted when inferences are made regarding the potential causal association between playing contact sports like football and CTE.

In fact, it is unethical to claim that simply because this is a case series study, it is inappropriate to share with athletes the results of this study during a discussion of their potential risk for long term negative health effects. While a clinician who does not view this incredibly large case series as *evidence of causality* may choose to frame the discussion within that personal perspective, it is the responsibility of the clinician to provide the athlete with up to date information from peer-reviewed research in order to enable the athlete to make an informed decision regarding their health. To hide the results of such studies from an athlete, simply because they are case studies, effectively bars the athlete from making informed decisions regarding their own health.

Cassidy describes himself as an expert in systematic reviews and thus unsurprisingly claims that systematic reviews provide more appropriate conclusions regarding causality. However, the systematic reviews of the sports-related concussion literature co-authored by Cassidy utilize overly restrictive inclusion criteria. By limiting their evaluation to only a small fraction of the existing studies these systematic reviews are themselves deeply flawed by selection bias. This "cherry picking" of only those study designs he personally approves of coupled with his discounting of the value of Hill's Criteria for Causation in making causal inferences result in Cassidy's failure to draw appropriate conclusions from the existing body of knowledge.

Numerous other researchers conducting systematic reviews do not believe in such overly restrictive inclusion criteria. The following are just two of multiple

examples of such recently published systematic reviews. In their systematic review of causal inference regarding infectious aetiology of chronic conditions, Orrskog et al, followed very similar methodology to that of the systematic reviews co-authored by Dr. Cassidy (e.g., their literature review included multiple datasets, they conducted their critical appraisal of the included publications using study design-specific Scottish Intercollegiate Guidelines Network [SIGN] checklists, etc.) yet, in their systematic review these authors included not only systematic reviews and randomized controlled trials, but cohort studies, cross-sectional studies, case-control studies, case studies/case series/case reports, non-systematic literature reviews, and pathological assessments of diseased material (Orrskog S, Medin E, Tsolova S, and Semenza JC. Causal inference regarding infectious aetiology of chronic conditions: a systematic review. PLoS One. 2013; 8(7):e68861).

In a study of the evidence for the effectiveness of minimum pricing of alcohol policy interventions, Boniface et al conducted a systematic review that also followed very similar methodology to that of the systematic reviews co-authored by Cassidy (e.g., their literature review included multiple sources, they conducted their critical appraisal of the included publications according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines, etc.) yet, in their systematic review these authors also included "any study design" (Boniface S, Scannell JW and Marlow S. Evidence for the effectiveness of minimum pricing of alcohol: a systematic review and assessment

using the Bradford Hill criteria for causality. BMJ Open. 2017;7(5):e013497). These are but two studies that clearly indicate Cassidy's assertions regarding the appropriateness of including a wider range of study methodologies when reviewing the literature and assessing its quality is not held by all other researchers conducting systematic reviews.

In fact, even if one restricts the analysis of the literature to a strong systematic review using Cassidy's overly restrictive criteria a recently published systematic review of potential long-term effects of sport-related concussion can be found in which a group of researchers, that included Dr. Christopher Randolph (another of defendant's experts), followed Cassidy's criteria for a strong systematic review by ensuring: 1) the study reviewed papers from multiple databases – even engaging a health sciences librarian using the CADTH Peer Review Checklist for Search Strategies, 2) the study had strict study selection criteria described using a PRISMA diagram, and 3) the study assessed risk of bias and level of evidence using the Downs and Black checklist. (Manley G, Gardner AJ, Schneider KJ, Guskiewicz KM, Bailes J, Cantu RC, Castellani RJ, Turner M, Jordan BD, Randolph C, Dvorak J, Hayden KA, Tator CH, McCrory P, and Iverson GL. A systematic review of potential long-term effects of sport-related concussion. Br J Sports Med. 2017;51(12):969-977). That strong systematic review of 3,819 studies, of which 47 met the inclusion criteria, found "Some former athletes have depression and cognitive deficits later in life, and there is an association between these deficits and multiple prior concussions." And "Some

retired professional American football players may be at increased risk for diminishment in cognitive functioning or mild cognitive impairment (several studies), and neurodegenerative diseases (one study)." Similarly, another recently published systematic review concluded, "There is strong evidence that a history of concussion in American football players is associated with depression later in life and short-term physical dysfunctions." (Vos BC, Nieuwenhuijsen K, and Sluiter JK. Consequences of traumatic brain injury in professional American football players: a systematic review of the literature. Clin J Sport Med. 2017;May 9:doi 10.1097 epub ahead of print.)

Thus, even when the vast majority of the published literature is ignored in order to meet Cassidy's unreasonably restrictive requirements, there is still evidence that athletes who have experienced a concussion are at increased risk of long term negative health effects. Perhaps even more disturbing is Cassidy's lack of acknowledgement of previously published systematic reviews that *disagreed* with the findings of his own systematic reviews. For example, a systematic review commissioned by the American Academy of Neurology found evidence of severe or prolonged early post-concussion impairments and chronic neurobehavioral impairments. (Giza C, Kutcher JS, Ashwai S, Barth J, Getchius TS, Gioia GA, Gronseth GS, Guskiewicz K, Mandel S, Manley G, McKeag DB, Thurman DJ, and Zafonte R., Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology.

2013;80(24):2250-7.) For example, in a subsection titled "Predictors of severe or prolonged early post-concussion impairments" the authors concluded "It is highly probable that ongoing clinical symptoms are associated with persistent neurocognitive impairments demonstrated on objective testing (1 Class I study, 2 Class II studies). There is also a high likelihood that history of concussion (3 Class I studies, 2 Class III studies) is associated with more severe/longer duration of symptoms and cognitive deficits" while in another subsection titled "Predictors of chronic neurobehavioral impairment" the authors concluded "Prior concussion exposure is highly likely to be a risk factor for chronic neurobehavioral impairment across a broad range of professional sports, and there appears to be a relationship with increasing exposure (2 Class I studies, 6 Class II studies, 1 Class III study) in football, soccer, boxing, and horse racing."

c. <u>There are "high quality" studies that support the conclusion that concussions lead to an increased risk of LTNDs</u>

Cassidy's assertion that there are no high quality studies on this topic relies solely upon Cassidy's personal opinion regarding the definition of "high-quality confirmatory studies." (Cassidy ¶¶ 25-26). There is widespread agreement among epidemiologists regarding relative strengths and weaknesses of various study designs, as well as the traditionally step-wise progression through study designs from case series to cross sectional to case control to cohort to either RCTs or prospective longitudinal cohort. However, relative strength of study methodology is not analogous to quality. It is simply not appropriate to conclude that most

epidemiologists would not contend that a well-conceived cross sectional study that mitigates, to the extent possible, bias and which was conducted in a large sample providing adequate statistical power would be considered to be higher quality than a poorly conceived cohort study that failed to take available actions to mitigate known biases and which used a sample size too small to achieve adequate statistical power.

d. Cassidy erroneously concludes that the medical literature does not support a causal relationship between concussion and LTNDs

Cassidy concludes there are very few low risk of bias studies on MTBI and LTNDs and thus there is no support in the medical literature that one can lead to the other. (Cassidy ¶¶ 27-29). Again, this is an overstatement resulting from Cassidy's overly restrictive definition of "reliable or valid scientific evidence." It is quite interesting to me that Cassidy chooses to simply discount any study he feels is not "low risk" of bias when *all* study designs (even RCTs) have bias risk. It is not appropriate from a scientific perspective to simply "cherry pick" those studies you choose to believe while discounting all studies you disagree with based simply on a rigid inclusion methodology. Rather it is inherent upon epidemiologists to evaluate the potential bias of *each* study and to subsequently determine how it may have affected the outcomes of interest and the author's conclusions. Finally, Cassidy contradicts himself in this paragraph, first saying "those that do, show mixed results, including studies that conclude there is no association between MTBI/concussions and LTNDs." which means there are also

studies that *do* show associations between MTBI/concussions and LTNDs, yet he then states that based on his review "there is no reliable or valid scientific evidence…"

All studies have strengths and weaknesses and are subject to various biases so Cassidy's assertion that none of the cited studies are of any value because of his personal belief that they are "high-risk of bias studies" is only that, his personal belief. For over 5 decades epidemiologists have utilized Hill's Criteria for causation to make causal inferences based on the accumulated body of knowledge. Cassidy dismisses this long valued practice to instead "cherry pick" only those studies he believes meet his personal standards for quality and ability to evaluate causality while discounting wholesale the vast majority of the quite large and rapidly growing body of knowledge on mTBI and LTNDs.

Most epidemiologists and clinicians will recognize the overwhelming evidence of an association between playing football and CTE found in the recently published JAMA paper by Mez et al. (Mez et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA. 2017;318(4):360-370). But Cassidy, I suspect, would opine this study be discounted completely because it is a case series study. This is counter to most epidemiologists and clinicians who would find the sheer sample size of this case series study coupled with the incredibly high prevalence of CTE in the studied former NFL players' brains to be more than sufficient to at least begin to infer causality.

e. Proper Application of Hill's Criteria for causation compels warnings to NHL players of the risk of LTNDs from concussions

Cassidy states that based on the current state of medical literature "there is no basis for clinicians or regulators to warn athletes about LTNDs or to make policy changes that address any potential long-term risks." (Cassidy ¶31). This is the most disturbing statement made in Cassidy's Declaration and, frankly, it is incredibly irresponsible for him to claim there is no basis for clinicians or regulators to warn athletes about their potential risk simply because he has not yet been personally satisfied by the large body of knowledge. At this point it is necessary to provide a rather lengthy response regarding Cassidy's gross dismissal of the highly valued application of Hill's Criteria for Causation.

Hill's Criteria, first widely publicized during an address to the Royal Society of Medicine, included nine aspects of association which, although never intended to be viewed as rigid criteria for causation, have been widely adopted and valued over the past half-decade as guidance for making causal inferences. While there has been ongoing debate over the utility of Hill's Criteria, even opponents to their use have acknowledged that the publication of his address is one of the most cited papers in health research, that the resulting Hill's Criteria are still widely taught to students of epidemiology, and that Hill's Criteria is invoked more often than any other method for assessing causation (Phillips CV and Goodman KJ. The missed lessons of Sir Austin Bradford Hill. Epidemiol Perspect Innov. 2004;1:3.).

In 1965, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics at the University of London, in the President's Address to the Proceedings of the Royal Society of Medicine began his discussion of causation with the following statement, "I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unraveled or a few links may suffice. It will depend upon circumstances."

Hill then proceeded to outline the foundational concepts of criteria for causation upon which epidemiologists across the world continue to refer to even today by saying "Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?" The nine criteria he then discussed became known simply as Hill's Criteria for Causation:

1. Strength

a. In this section Hill demonstrates his point by discussing the fact that death rate from lung cancer in smokers was nine to ten times higher than the lung cancer death rate in non-smokers and that the rate in heavy cigarette smokers was twenty to thirty times as great. He noted, "Though there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand-in hand with smoking – features that might conceivable be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic 'you can't prove it, there *may* be such a feature'."

b. Hill continued saying, "Certainly in this situation I would reject the argument sometimes advanced that what matters is the absolute differences between the death rates of our various groups and not the ratio of one to the other. That depends upon what we want to know. If we want to know how many extra deaths from cancer of the lung will take place through smoking (i.e., presuming causation), then obviously we must use the absolute difference between the death rates… But it does not follow here, or in more specifically occupational problems, that this best measure of the effect upon mortality is also the best measure in relation to aetiology. In this respect the ratios of 8, 20 and 32 to 1 are far more informative."

2. Consistency

a. In this section Hill noted, "This requirement may be of special importance for those rare hazards singled out in the Section's terms of reference."

b. He went on to state, "We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the original evidence; yet the same results from precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would

myself put a good deal of weight upon similar results reached in quite different ways, e.g. prospectively and retrospectively."

3. Specificity

    a. Hill was careful to emphasize that "In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence."

4. Temporality

    a. Hill opined, "This is a question which might be particularly relevant with diseases of slow development."

    b. Particularly relevant to the discussion of NHL players risk of concussion and subsequent long term negative health outcomes, Hill said, "This temporal problem may not arise often but it certainly needs to be remembered, particularly with selective factors at work in industry."

5. Biological gradient

    a. Hill noted the simplicity of this concept by stating "The clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light."

    b. He then went on to say "Often the difficulty is to secure some satisfactory quantitative measure of the environment which will permit us to explore this dose-response. But we should invariably seek it."

6. Plausibility

    a. In this section Hill admitted, "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day."

    b. However, he then went on to say, "In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd."

7. Coherence

    a. Hill explained this concept by saying, "On the other hand the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease…"

    b. In this section while discussing his interpretation of early histopathological evidence for the carcinogenic effect of cigarette smoking he noted, "Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed may determine the actual causative agent, the lack of such evidence cannot nullify the epidemiological observations in man."

    c. Additionally, while noting that John Snow's famous London Cholera investigation and his conclusions regarding cause (tainted water from the Broad Street pump) and effect (illness and death from cholera) were not at the time supported by indisputable microbiological evidence, Hill concluded, "Yet the fact that Koch's work was to be awaited another thirty years did not really weaken the epidemiological case though it made it more difficult to establish against the criticisms of the day – both just and unjust."

8. Experiment

    a. Here although hill noted that experimentation is not always possible, stating, "Occasionally it is possible to appeal to experimental, or semi-experimental, evidence."

    b. He admitted however, "Here the strongest support for the causation hypothesis may be revealed."

9. Analogy

    a. For this last criteria he simply stated, "In some circumstances it would be fair to judge by analogy. With the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy."

Even recent critiques regarding how the Hill's Criteria should be applied in the 21st century have concluded that the Hill's Criteria are far from outdated in a data integration framework and that, while the specific interpretations of each of the nine criteria have evolved over time, the concepts that underlie each can still be applied to a variety of methodologies to answer questions about causation (Fedak KM, Bernal A, Capshaw ZA, and Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 2015;12:14).

The fact that Hill's Criteria are still so valued as guidance for making causal inference is evident in a continued stream of publications using them as a framework for assessing causality that continues even into 2017. A few examples of citations for studies utilizing Hill's Criteria to evaluate causality include the following very recently published papers:

1) In their study of take-home naloxone programs, Olsen et al determined that "The Bradford Hill criteria for assessing causality are useful in assembling evidence, including within complex policy analyses" and that "Hill's criteria offered a useful analytical tool for interpreting current evidence on THN programs and making decisions about the (un)certainty of THN program safety and effectiveness" (Olsen A, McDonald D, Lenton S, Dietze PM. Assessing causality in drug policy analyses: How useful are the Bradford Hill criteria in analyzing take-home naloxone programs. Drug Alcohol Rev. 2017 Apr 18 doi: 10.1111/dar.12523 [Epub ahead of print]).

2) Showing the value of utilizing Hill's Criteria to evaluate causality when only "four case-control studies and one retrospective epidemiological study" had reported an association between humidifier disinfectants and lung injury, Ha et al concluded that after "A careful examination on the association between the HDs and lung

injury was based on the criteria of causality inference by Hill and the US Surgeon General Expert Committee" those few studies proved "the strong association between the use of the HDs and lung injury, based on scientific evidence" (Ha M, Lee SY, Hwang SS, Park H, Sheen S, Cheong HK, Choi BY. Evaluation report on the causal association between humidifier disinfectants and lung injury. Epidemiol Health. 2016;38:e2016037).

Examples with similarity to issues of pertinence to this discussion (e.g., suicide, cognitive decline, and dementia are three of several potential negative health effects associated with sports-related concussion.) include:

1) Large et al stated they "used the framework of Austin Bradfor Hill's criteria for causality in epidemiology to consider the possibility that psychiatric hospitalization might causally contribute to the extent and variation in in-patient suicide rates" in their 2017 paper (Large MM, Chung DT, Davidson M, Weiser M, and Ryan CJ. In-patient suicide: selection of people at risk, failure of protection and the possibility of causation. BJPsych Open. 2017;3(3):102-105).

2) McCaddon and Miller reviewed the evidence of two reports assessing the cumulative epidemiological evidence for hyperhomocysteinemia as a risk factor for cognitive decline and incident dementia in older adults "in relation to Sir Austin Bradford Hill's criteria for assessing 'causality'…" (McCaddon A and Miller JW. Assessing the association between homocysteine and cognition: reflections on Bradford Hill, meta-analyses and causality. Nutr Rev. 2015;73(10):723-35).

3) Miklossy critically analyzed the association and causal relationship between spirochetes and Alzheimer's disease following "established criteria of Koch and Hill" (Miklossy J. Alzheimer's disease – a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation. 2011;8:90).

Important systematic reviews utilizing Hill's Criteria include:

1) Orrskog et al conducted a systematic review regarding infectious aetiology of chronic conditions closely following the methodology of the systematic reviews cited by Cassidy, in which they evaluated the number of Hill's criteria of causation and Koch's postulates that

were fulfilled by the included studies as one component of their determination of causality (Orrskog S, Medin E, Tsolova S, and Semenza JC. Causal inference regarding infectious aetiology of chronic conditions: a systematic review. PLoS One. 2013; 8(7):e68861)

2) Boniface et al conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and assessed the studies "against the Bradford Hill criteria for causality" to assess the evidence for the effectiveness of price-based alcohol policy interventions (Boniface S, Scannell JW and Marlow S. Evidence for the effectiveness of minimum pricing of alcohol: a systematic review and assessment using the Bradford Hill criteria for causality. BMJ Open. 2017;7(5):e013497).

Even a recent meta-analysis restricted to prospective population-based studies utilized Hill's Criteria as follows:

1) In their meta-analysis evaluating the "independent association and causality between anxiety and incident CVD" although Batelaan et al restricted the studies eligible for inclusion to prospective population-based studies they still utilized Hill's Criteria "to examine the likelihood of causality in the association between anxiety and new-onset CVD" and they concluded "An important strength of this study is the integration of a quantitative summary (meta-analysis) and a qualitative assessment (application of Hill's criteria for causality)." (Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, and Pennix BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. Br J Psychiatry. 2016;208(3):223-31).

As evidenced in both my and Dr. Cantu's reviews of the existing body of knowledge, Hill's Criteria for Causation can be applied to infer causality with respect to the associations between 1) playing in the NHL and increased risk for concussion, and 2) sports-related concussion and long term negative health effects. Thus, as Hill concluded at the end of his presentation before the Royal Society of Medicine, "All scientific work is incomplete – whether it be observational or

experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time." (All direct quotes above are referenced to Hill AB. The Environment and Disease: Association or Causation? President's Address to the Proceedings of the Royal Society of Medicine. Jan 14, 1965.)

Cassidy's claim that clinicians and regulators should be required to wait for definitive proof of causality from prospective longitudinal studies that would take decades to conduct before discussing with athletes their potential risk of long term negative health effects and before implementing measures to better safeguard athletes' health seems both irresponsible and dangerous. Over 50 years ago, Hill understood the potential ramifications of erroneously concluding causality when, in fact, a causal association does not exist but he asserted such concerns should not drive individuals to inactivity pending certainty. Specifically he stated, "Finally, in passing from association to causation I believe in 'real life' we shall have to consider what flows from that decision. On scientific grounds we should do no such thing. The evidence is there to be judged on its merits and the judgment (in that sense) should be utterly independent of what hangs upon it – or who hangs because of it. But in another and more practical sense we may surely ask what is involved in our decision. In occupational medicine our object is usually to take action."

He illustrated his point using an example of scientists using "relatively slight evidence" deciding to restrict a drug for morning sickness in pregnant women saying, "If we are wrong in deducing causation from association no great harm will be done. The good lady and the pharmaceutical industry will doubtless survive."

The direct and unavoidable analogy for us today is that we have more than adequate scientific grounds to take action by having physicians inform NHL players of our concerns for their long term health and by having regulators (i.e., the NHL) implement additional efforts to decrease NHL players' risk of sustaining a sports-related concussion. If such actions are taken and our assertions are subsequently disproven, both the athletes and the NHL will doubtless survive. However, if our assertions are ultimately proven but we have ignored the existing and rapidly growing evidence until undisputed causality could be demonstrated to even the most ardent critic's satisfaction utilizing Dr. Cassidy's personal opinions regarding study quality, athletes will undoubtedly suffer.

Finally, in anticipation of Cassidy simply dismissing all of the above discourse on the value of Hill's Criteria as being outdated, I refer to a modern discussion of causal inference (Glass TA, Goodman SN, Hernan MA, and Samet JM. Causal inference in public health. Annu Rev Public Health. 2013;34:61-75.). In this discussion the authors note that in an ideal world causal inference would be based on comparisons of the distribution of health outcomes after different interventions in randomized experiments and that all public health decisions would

be based on the findings of such experiments (quite similar to the procedure called for by Cassidy).

However, they then acknowledge that experimental studies are often unethical, impractical, or too lengthy for timely decision making and that "As a result, causal inferences for public health are usually derived from observational studies, buttressed by other lines of evidence if available." The authors do acknowledge that the use of observational, rather than experimental, studies for causal inference in public health does raise concerns, but they assert that these concerns can be mitigated by review of findings from well-designed observational studies.

Further while the authors discuss the limitations of Hill's Criteria, they also assert that "Today, public health practice can be seen to be influenced by both the classic and modern frameworks…" and note that the International Agency for Research on Cancer of the World Health Organization, which conducts systematic reviews to classify agents by their carcinogenicity, evaluates evidence "with an approach based in the Hill or classic criteria." They also state "The challenge of determining causation in public health has always been shaped by the limitations of the available data, the understanding of the underlying biological or sociological processes, and our ability to intervene in the real world. Faced with sometimes limited data and often poor understanding of a network of connected factors in a complex world, we revert to pragmatism." In other words, interpreting causality is not a simple, well-defined endeavor and it is not appropriate to refrain

from taking public health action until perfect data exists. That would simply be reckless.

f. Cassidy's concerns about iatrogenic effects are unfounded

Cassidy suggests that ongoing publicity about "brain damage" following MTBI may actually be hindering recoveries. (Cassidy ¶ 32). But it is ironic that after Cassidy's assertions there is not sufficient evidence to make any statements regarding sports-related concussions and risk of long term health effects, he then makes a wholly unsupported claim that publicity "may have a deleterious effect on recovery after MTBI/concussion." (Cassidy ¶ 32). Additionally, if Cassidy's previously stated contention is that it is currently impossible to measure athletes' risk of concussion related negative health effects including stress, anxiety, and depression, then how can he possibly accurately measure the potentially iatrogenic effects of anxiety, depression, and suicide attributed to athletes' worry regarding their symptoms? In other words, how can Cassidy possibly separate anxiety, depression, and suicide that are attributed to athletes worry about their concussion symptoms from the anxiety, depression, and suicide that are actually caused by their concussion? Here again, he is simply "cherry picking." To claim here that there is such a strong concern regarding potential negative effects of worry over an injury that actions should be taken (in this case limiting publicity) by researchers, clinicians, and policy makers – despite a lack of any scientific evidence to support such an assertion – when in the paragraph above he so strongly asserted that

clinicians and policy makers should be prohibited from taking any action (in that case educating athletes or taking steps to better safeguard them) because the large and still growing body of scientific evidence has not yet met his personal standards demonstrates a dichotomy that is simply hypocritical. Moreover, Cassidy ignores the simple fact that the antidote for iatrogenic illness is *more* information about potential effects, not *less* information.

2. *Responses to Section IV of Dr. Cassidy's Declaration*

In this section, Cassidy offers an incredibly brief primer Introduction to Epidemiology. (Cassidy ¶¶ 33-44). While it is for the most part an adequate overview, it is also another example of his tendency to "cherry pick" only those facts that support his position. For example, he mentions epidemiologists' responsibility to evaluate bias at paragraph 33, while ignoring epidemiologists' responsibility to drive transition of knowledge into practice. This section again displays Cassidy's tendency to present his personal opinion of how otherwise broadly accepted knowledge should be restricted based on his definitions and determinations of quality. For example, in paragraph 36 he inappropriately asserts that *all* prevalence studies are cross-sectional studies, which is simply untrue.

Throughout this section Dr. Cassidy also *overstates* the quality of those studies he prefers. For example, in paragraph 38 he claims that incident cohort studies include all cases of the disease, whereas cross-sectional studies only include available cases, which is another untruth. A poorly designed cohort study that suffers from sample selection bias or data acquisition problems (e.g., one that

relied wholly upon self-report of an outcome without any medical record support) will not include all cases of the outcome of interest in the study population, while a well-designed cross-sectional study in a large generalizable sample that utilizes medical record support of lifetime history of an indisputable outcome of interest (e.g., cesarean delivery) can definitely capture all cases in the study population. Cassidy's assertion in paragraph 38 that prevalence surveys should not be used to infer causation again blatantly ignores the highly valued use of preponderance of evidence (e.g., application of Hill's Criteria) to make causal inferences, and the role that prevalence surveys, when combined with additional studies, can play in helping to establish that preponderance of evidence.

Another misstatement by Cassidy that appears intended to support his assertion is his contention in paragraph 39 that presence of disease may influence recall of exposure in cross-sectional studies without also acknowledging that presence of exposure may influence the measure of outcome in a cohort study (e.g., in a study designed to evaluate the effect of an educational intervention study on a student athletes risk of a health outcome that must be self-reported, those athletes whose parents also read the educational material may be more likely to report the outcome than those whose parents did not also read the educational material).

Cassidy also tends to report common practices as unbendable facts. For example, in paragraph 40 he states risk-ratios can only be calculated from cohort studies when, in some circumstances, risk-ratios can also be calculated from other

study designs such as ecological studies and meta-analyses. In that same paragraph Cassidy correctly notes that the risk-ratio is a measure of risk, which contradicts his contention in paragraph 20 that to measure risk one must calculate an AR. Rather, as he notes in paragraph 41, both the risk-ratio (RR) and attributable risk (AR) can be used to measure risk. They simply measure slightly different concepts of risk.

In paragraph 42 Cassidy proffers an illogical assertion regarding the ability to calculate ARs which is actually central to his earlier assertions regarding the inability to make causal inferences until one calculates ARs. In paragraph 42 Dr. Cassidy follows the following lines of statements: 1) most health conditions, like lung cancer, have multiple causes, 2) smoking is a risk factor for lung cancer, 3) risk of lung cancer is increased in those exposed to asbestos, 4) to determine the attributable risk of lung cancer due to asbestos exposure one must know the incidence in the exposed and unexposed group, 5) smoking may be a confounder of the association between asbestos and lung cancer, 6) smoking needs to be accounted for to obtain an accurate estimate of the risk of lung cancer due to asbestos exposure, and 7) all potential confounding factors need to be measured and adjusted for in the analysis of risk factors. The basic flaw is the circular logic is that you must know the risk associated with every exposure of interest for lung cancer (i.e., smoking, working in a coal mine, living in an area with very high levels of pollution, etc.) and control for each of them in order to accurately measure true risk of another exposure (i.e., asbestos) which then makes it

impossible to measure the risk of any of the exposures since you are never able to accurately measure the risk of the first. After all, how does one ever accurately measure risk associated with any exposure of interest since the measure of each exposure's risk is dependent upon an accurate measurement of all the others? The point here is that Cassidy makes this assertion regarding the only correct way to measure risk when it simply is not feasible in the real world settings in which epidemiologists actually work. It would be a very slow progression of science, virtually devoid of novel findings, if researchers were truly limited, as Cassidy contends in paragraph 43, to evaluating an exposure or potential risk factor only via "replication of well-designed studies that accurately measure and control for known risk factors, or potential confounding factors." Again, Cassidy's assertion demonstrates a far too narrow explanation of the capabilities of epidemiologic studies that, frankly, are simply not feasible in the real world.

Finally, in paragraph 44 Cassidy perhaps once again simply used an unfortunate word choice? Causal *assessment* can be made via a multitude of study designs, not simply the three noted here (e.g., ecological studies, meta-analyses, systematic reviews, etc.).

3. *Responses to Section V of Dr. Cassidy's Declaration*

Throughout this section (Cassidy ¶¶ 45-78), which is further broken into two subsections, Cassidy continues to provide his narrow and biased perception of the current state of epidemiologic techniques. He relies throughout upon flawed, incomplete, and/or inaccurate conclusions to support his assertions. Although

those instances are legion, only a small number of examples are needed to explain why his approach is flawed.

First, Cassidy's Fig. 1 (display of the hierarchy of causal evidence) appears to be of his own design (he provides no citation to an epidemiologic textbook and I have not seen this version previously). More concerning, it is rife with misstatements or personal statements. For example, the NIH annually funds numerous basic science studies that are hypothesis testing – to contend that all basic science studies are merely hypothesis generating is not only false, it is absurd. While I agree with the widely accepted progression of strength of study design from case reports/series to cross-sectional studies to case-control studies to cohort studies to RCTs (which are actually an advanced sub-type of cohort study), it is not accurate to claim that systematic reviews (a study design Cassidy claims expertise in) are higher quality than RCTs. Nor is the breakpoint between hypothesis generating and hypothesis testing absolute as indicated. Finally, as previously discussed, Cassidy's conflating of strength of study design with ability to draw causal inferences is his personal opinion, not a matter of established scientific methodology.

Second, Cassidy again displays his penchant for making sweeping statements he then presents as facts that are at best oversimplifications and at worst false statements. For example, in paragraph 48 Cassidy states "However, any associations between exposures and prevalent cases in a cross-sectional study are hypothesis-generating only because of issues of temporality (i.e., exposures

and outcomes are measured at the same time) and selection bias (i.e., prevalence/incidence bias)." While this is largely the case in cross-sectional studies it is not an absolute as Cassidy asserts. For example, while cross-sectional studies do measure exposure and outcome at the same point in time, that does not mean that the temporality of exposure and outcome can never definitively be demonstrated. For example, multiple population based cross-sectional studies report findings based on birth data (e.g., birth weight, prematurity, etc. – items easy to definitively capture from birth records) and subsequent health outcomes (e.g., childhood obesity, maternal post-partum depression, etc.) or on childhood related variables (e.g., zip code of residence, being raised in home that was occupied by at least one smoker, etc.) and subsequent adult health outcomes (e.g., every having had a dental carry requiring a filling, ever being diagnosed with asthma, etc.). Thus, once again, Dr. Cassidy's wide-sweeping assertions regarding the inability of cross-sectional studies to ever demonstrate temporality or to ever consist of samples free from selection bias, while very frequently the case, are in no way absolute truths.

Third, paragraphs 54 and 55 demonstrate Cassidy's own biased opinions regarding systematic reviews (it must be noted here this is a study design he claims to have expertise in). First it is worth noting that Cassidy does not provide a citation to support his assertion that systematic reviews are placed at the top of the causal hierarchy. Second it must be noted here that Cassidy fails to provide any weaknesses/limitations of systematic reviews as he provided above for all

other study designs discussed. This is not because systematic reviews are devoid of any weaknesses. In fact, systematic reviews suffer from many of the same biases Cassidy noted as weaknesses of other study designs. For example, systematic reviews are subject to sample bias if the literature search is not conducted across an appropriately wide range of datasets. Just as cohort studies are more difficult to conduct when studying rare diseases, so too are systematic reviews due to the relative paucity of studies available to review. Systematic reviews are also susceptible to selection bias if the inclusion criteria used to identify studies to be reviewed is too narrow or if the exclusion criteria is too wide.

Fourth, Cassidy states "A good systematic review would exclude hypothesis-generating studies like case reports, case series, cross-sectional studies, basic science studies and expert opinion, as these studies cannot provide evidence-based conclusions regarding causation" (Cassidy ¶ 55), but that is simply his personal interpretation/preference rather than a widely accepted scientific methodology. Numerous other researchers conducting systematic reviews do not believe in such overly restrictive inclusion criteria. The following are just two of multiple examples of such recently published systematic reviews that belie Cassidy's sweeping statement:

> 1. In their systematic review of causal inference regarding infectious aetiology of chronic conditions, Orrskog et al, followed very similar methodology to that of the systematic reviews co-authored by Cassidy (e.g., their literature review included multiple datasets, they conducted their critical appraisal of the included

> publications using study design-specific Scottish Intercollegiate Guidelines Network [SIGN] checklists, etc.) yet, in their systematic review these authors included systematic reviews, randomized controlled trials, cohort studies, cross-sectional studies, case-control studies, case studies/case series/case reports, non-systematic literature reviews, and pathological assessments of diseased material (Orrskog S, Medin E, Tsolova S, and Semenza JC. Causal inference regarding infectious aetiology of chronic conditions: a systematic review. PLoS One. 2013; 8(7):e68861).
>
> 2. In a study of the evidence for the effectiveness of minimum pricing of alcohol policy interventions, Boniface et al conducted a systematic review that also followed very similar methodology to that of the systematic reviews co-authored by Cassidy (e.g., their literature review included multiple sources, they conducted their critical appraisal of the included publications according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines, etc.) yet, in their systematic review these authors included "any study design" (Boniface S, Scannell JW and Marlow S. Evidence for the effectiveness of minimum pricing of alcohol: a systematic review and assessment using the Bradford Hill criteria for causality. BMJ Open. 2017;7(5):e013497).

These examples clearly indicate that Cassidy's assertions regarding the appropriateness of including a wider range of study methodologies when reviewing the literature and assessing its quality is not held by all other researchers conducting systematic reviews.

Fifth, it was concerning to see Cassidy's use of the term "confounding bias" in paragraph 63. Confounding and bias are two quite distinct epidemiologic constructs and they are not commonly merged as he has done here. It is quite important to retain the distinction for several reasons. For example, while epidemiologists have strategies for limiting the influence of bias on their studies, it is not always possible to objectively test the magnitude of the effect of bias on a

study, and it is often difficult, if not impossible, to control for biases in the analyses phase of a study. Conversely, confounding can be tested for and can also be controlled for either through study design (e.g., matching in case-control studies, etc.) or during data analyses (e.g., stratified analyses, etc.). Additionally, Cassidy once again makes a sweeping statement that simply does not reflect reality when saying "…all potential confounding factors need to be measured and controlled, or adjusted for, in the statistical analysis of risk assessment." In reality, it is possible only to control for *known* confounders and for confounders for which accurate data is available – thus, it is actually nearly always impossible for a researcher to truly control for *all potential* confounders since future research in the topic area may identify as yet unrealized confounding factors.

Sixth, paragraphs 64 and 65 provide the best insight into the extreme differences in the conclusions I and Cassidy reached from our review of the literature on sports-related concussions and the potential for long term negative health effects. I contend the systematic reviews cited here (which Cassidy co-authored) suffer severely from selection bias due to an overly restrictive study inclusion criteria, which inappropriately excluded the majority of peer-review publications in this field. While I took the widely approved and long valued epidemiologic approach of evaluating the entire range of peer-review publications and utilizing indicators of preponderance of evidence (including Hill's Criteria for Causation) in my conclusions regarding inference of causality, Cassidy instead decided that only a very small fraction of the available peer-review literature was

worthy of his review and thus, his conclusions are limited to that dramatically skewed sample. In other words, while I analyzed the entire body of research and used accepted methodology to select studies with more rigorous or relevant designs, Cassidy blindly excluded a huge body of well-designed studies to reach his conclusions. This distinction is particularly important in this instance because the types of studies Cassidy asserts are the only ones which may inform this issue either can't be conducted or will take several decades to conduct.

It is unethical to conduct RCTs (the most well respected study methodology) in which one group of randomly selected athletes would intentionally be concussed and then they and a randomly selected non-concussed group of athletes would be followed over time to compare rates of various negative health outcomes and it is simply not acceptable to wait for the 30 to 50 years it would take to conduct a prospective longitudinal study of NHL players. Thus, for Cassidy to ignore the large and growing body of knowledge in this field simply because these peer-reviewed publication (often published in highly respected medical journals) do not meet his personal criteria is misguided at best and intentionally biased at worst. It should also be noted that there is an important distinction between saying there is no evidence, as Cassidy has done by dismissing out of hand the existing body of literature, and saying there is not yet definitive proof of causality based on RCTs or prospective longitudinal studies. The former is simply untrue.

Seventh, in paragraphs 66 through 78 Cassidy demonstrates his disdain for Hill's Criteria for Causation, ironically missing Hill's own intention for the utilization of his Criteria. Hill summarized his 9 presented criteria thusly, "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" So, Cassidy has gone to great lengths to try to explain away the large and still expanding body of literature which I believe clearly demonstrates that full contact athletes (including football and ice hockey players) are at increased risk for concussion and, at the barest minimum, must be acknowledged as strongly suggesting that those who sustain sports-related concussion are at increased risk of subsequent long term negative health effects. What Cassidy has failed to do is to address the fundamental question posed by Hill – is there any other way of explaining the set of facts before us, is there any other answer equally, or more likely than cause and effect?

4. *Responses to Section VI of Dr. Cassidy's Declaration*

This section (Cassidy ¶¶ 79-84) should largely be discounted for two reasons: 1) it is based on the extremely restrictive and biased inclusion/exclusion criteria of the systematic review methodology favored by Cassidy, which completely ignores/discounts the vast majority of the published body of

knowledge while applying subjective critiques of study biases and strengths and weaknesses, and 2) Cassidy is overstating the importance of the impact of the work in the field, perhaps in an attempt to overstate the appropriateness of his expertise. For example, the fact the Karolinska Institute awards the Nobel Prize in Physiology or Medicine each year is completely irrelevant to the question of the causal association between playing contact sports and subsequent long-term negative health outcomes. A review of Cassidy's CV indicates he had done very little research on sports-related concussions prior to his involvement in this WHO Task Force – his area of expertise was largely in motor vehicle and occupational back/spine injuries although he did also do some research on motor vehicle and occupational TBI/mTBI – raising the question of why an epidemiologist with more specific experience in sports-related mTBI was *not* involved in the project. After all, one of the defendants' experts' many rationales for discounting as much of the published peer-review literature as possible is to claim that football injuries are not generalizable to ice hockey injuries and thus, findings from studies of football players should be excluded. Of course, ice hockey injuries are undoubtedly much more similar to football injuries than they are to motor vehicle injuries or occupational injuries which, if anything, rather than calling into question the many papers reporting on football players, should perhaps call into question Cassidy's specific content area expertise.

5. *Responses to Section VII of Dr. Cassidy's Declaration*

This section (Cassidy ¶¶ 85-90) should largely be discounted for the same two reasons: 1) because the same suspect methodology was utilized in this follow up systematic review it suffers from the same weaknesses and biases as the original WHO sponsored study, and 2) Cassidy's overstatement of the importance of this work takes on an additional odd turn in this section where he repeatedly intimates that this updated review was also WHO sponsored work although that was not the case. Just because some of the collaborators of the WHO sponsored work also collaborated on this work and the researchers asserted that it was an update to the WHO sponsored work, this subsequent research was not in fact a WHO study. To write this section in a way that can be so easily misinterpreted as if it was a WHO study is at a minimum poor writing, and at worst intentionally misleading.

6. *Responses to Section VIII of Dr. Cassidy's Declaration*

This section (Cassidy ¶¶ 91-94) is disappointing for a few reasons. First, one would expect that an expert in systematic reviews who so adamantly contends that only a very exacting, thorough review of the literature following very restrictive systematic review methodology is appropriate when evaluating the current state of knowledge would have updated his prior work with the last few years of additional data when asked to provide his professional opinion of the current state of knowledge. Rather than doing so, Cassidy states he simply reviewed the literature cited by myself and Dr. Cantu – the very literature he

personally believes is so lacking. This is particularly interesting given Cassidy's complaint that my literature review was not exhaustive enough.

Additionally, as noted above, there are more recently published systematic reviews which contradict the findings of Cassidy's systematic reviews which he fails to acknowledge. Finally, as mentioned above, Cassidy's failure to change his opinion regarding the quality of published literature and the evidence for a causal relationship is rooted in his overly narrow view of criteria for causality.

7. *Responses to Section IX of Dr. Cassidy's Declaration.*

Throughout this section (Cassidy ¶¶95-120) Cassidy simply continues to rely upon his overly narrow interpretation of assessment of causation as he discounts any study which does not meet his personally held beliefs of what type of study should be included in a systematic review (i.e., his believe that no case series, cross-sectional, or case control studies regardless of size, generalizability of the study sample, or methodological strength is worthy of being considered). I have responded to both issues above. However, while a point by point response of this section is therefore not warranted, a few of Cassidy's statements must be addressed.

Cassidy's assertion in paragraph 95 that I ignored hypothesis confirming studies is an unfair characterization. In fact, quite the opposite is true – whereas I reviewed the broad spectrum of information available, regardless of the study design, Cassidy admittedly refrained from even reviewing several classes of study designs in his systematic reviews. It is true that I did not cite and discuss each and

every publication on concussion in general or sports-related concussion specifically. To do so would have taken years and would have resulted in a report that was many hundreds of pages long. So, just as Cassidy makes his professional interpretation regarding which of the large number of available studies should be discussed in his systematic reviews, I similarly made my professional determination regarding which publications were most pertinent and important in my Declaration. I purposefully did not include systematic reviews in my Declaration because they simply do not represent original research, but rather are literally only a research teams' interpretation of the available literature. I would much rather go back to the original sources and read them myself, making my own professional evaluation of the strengths and weaknesses of each study and my interpretation of the importance of the original authors' conclusions rather than to rely upon another researcher's/research team's unavoidably subjective interpretation of that original work. However, due to Cassidy's strong opinions regarding the importance he believes should be placed on systematic reviews I have subsequently, above in this rebuttal, provided citations for several systematic reviews which call into question both Cassidy's assertions regarding the appropriate way to conduct a systematic review, as well as the actual conclusions of his systematic reviews of the literature on concussions.

It is incredibly hypocritical in paragraphs 97-99 that Cassidy takes me to task for what he claims is an unacceptable cursory and narrative review of the literature when in Section VII of his report, Cassidy clearly states that "I have not

personally conducted a systematic review of the literature on MTBI or concussions and subconcussive blows in sports since February 2012." Given this statement, Cassidy's entire Declaration must be called into question. If, as he contends, the only way to conduct an evaluation of the literature to provide a methodologically sound appraisal of the current state of knowledge is to conduct a systematic review then, by definition, his Declaration simply cannot be considered a reliable evaluation of the current state of knowledge in this field.

In paragraph 98, Cassidy makes yet another untruthful assertion when he states my review covered only the last decade and was limited to sports injuries only. The factual inaccuracy of this statement is clearly demonstrated in several subsequent points (e.g., ¶¶ 106, 107, 108, etc.) where Cassidy provides his opinions of the weaknesses of several studies I discuss in my Declaration which are *not* sports injury studies and/or are not limited to the last decade. It is difficult to tell if such an error is an indication of carelessness in the preparation of his report or an intentional attempt by Cassidy to unfairly tarnish my review of the literature.

In paragraph 99, Cassidy expresses his surprise at what he perceives to be the poor quality of my review. Apparently, we both share similar concerns about the other's work. While my review considered the entire body of relevant research, Cassidy limited his review in a biased way that relied entirely on the type of study rather than the strength of the study, ignoring multiple studies which would yield important results for the particular issues here, and thus, his review

appears designed to reach a predetermined result. Considering his overly narrow and assertively subjective view of the strengths and limitations of study designs specifically and epidemiology generally, I too am concerned regarding his training of future epidemiologists given his adamant disrespect for long valued epidemiologic tenants such as applying guidelines like Hill's Criteria for Causation to make causal inferences based on a preponderance of the evidence in order to take action to improve the health/safety of at risk populations when benefits likely outweigh risks, rather than waiting until after the "perfect" study is conducted to affect change.

Conclusion to Cassidy Rebuttal

Perhaps our differences lie in my training as an applied public health epidemiologist via the CDC's EIS program, in addition to my traditional doctoral level epidemiologic education, as opposed to Cassidy's training as chiropractic clinician in addition to his traditional doctoral level epidemiologic education. Regardless, the root difference between our two reviews and our conclusions regarding the current state of knowledge is that I am convinced that a sufficient body of knowledge exists to state that NHL players are at increased risk of concussion and that NHL players who sustain concussions are at increased risk of negative long term health effects. I am convinced that a well-designed medical monitoring program will serve both to help current retired NHL players (e.g., earlier diagnosis, better access to care, additional knowledge upon which to make quality of life and medical care decisions) and also to provide opportunities to

conduct the very type of research that could one day drive treatments as well as more effective prevention efforts. Further I am convinced there are immediate interventions which could reduce the risk of concussion among current NHL players without introducing any unintended health-related consequences (e.g., dramatically reducing fighting by increasing penalties and immediately enforcing the rules of the game rather than allowing players to drop their gloves and punch each other in the head). Therefore I see no sound scientific rational for putting off implementation of such concussion reducing interventions. Cassidy, on the other hand, claims only a decades long prospective longitudinal cohort study of NHL retired players and a suitable control group will suffice to convince him there is an adequate public health concern and he is unwilling to take any action to protect NHL players or improve the lives of retired NHL players until he is thusly satisfied.

B. Point by Point Response to Declaration of Christopher Randolph

1. *Responses to Dr. Randolph's Summary of Opinions*

In paragraph 18, Dr. Randolph claims, "There are no credible scientific data suggesting that retired athletes from any contact sport, including hockey, are at increased risk for any neurological or psychiatric condition either during their careers or during retirement." This statement is simply untrue and calls into question Dr. Randolph's review of the literature. Either his review was incomplete, he purposely neglected discussion of any studies that failed to support

his assertions (i.e., he "cherry picked" only those studies supporting his view), or he believes only he, rather than all of the peer-reviewers of the well-respected medical journals publishing these studies, is capable of determining what is "credible scientific data."

There are several examples of peer-reviewed studies that dispute Dr. Randolph's assertion, including the following. A large 2015 brain bank study (K.F. Bieniek *et al*., Chronic traumatic encephalopathy pathology in a neurodegerative disorders brain bank, 130 ACTA NEUROPATHOL. 6, 877-89 (2015)) clearly showed increased prevalence of CTE in contact sports athletes, including ice hockey players. A 2016 publication reported "A disproportionate number of completed suicides in current and former professional football players have occurred since 2009 (42.3%)" (Webner D and Iverson G. Suicide in professional American football players in the past 95 years. Brain Inj. 2016;30(13-14):1718-1721.). Similarly, a recently published systematic review concluded, "There is strong evidence that a history of concussion in American football players is associated with depression later in life and short-term physical dysfunctions." (Vos BC, Nieuwenhuijsen K, and Sluiter JK. Consequences of traumatic brain injury in professional American football players: a systematic review of the literature. Clin J Sport Med. 2017;May 9:doi 10.1097 epub ahead of print.).

Dr. Randolph himself was a co-author of a study of collegiate football players that concluded, "Our study suggests that players with a history of previous concussions are more likely to have future concussive injuries than those with no history…and previous concussions may be associated with slower recovery of neurological function." (Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W, Onate JA, and Kelly JP. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. JAMA. 2003;290(19):2549-55.). Additionally, even a systematic review co-authored by Dr. Randolph found "Some former athletes have depression and cognitive deficits later in life, and there is an association between these deficits and multiple prior concussions." And "Some retired professional American football players may be at increased risk for diminishment in cognitive functioning or mild cognitive impairment (several studies), and neurodegenerative diseases (one study)." (Manley G, Gardner AJ, Schneider KJ, Guskiewicz KM, Bailes J, Cantu RC, Castellani RJ, Turner M, Jordan BD, Randolph C, Dvorak J, Hayden KA, Tator CH, McCrory P, and Iverson GL. A systematic review of potential long-term effects of sport-related concussion. Br J Sports Med. 2017;51(12):969-977).

The publication of the studies co-authored by Dr. Randolph pose a particular problem for his contention that "There are no credible scientific data suggesting that retired athletes from any contact sport, including hockey, are at increased risk for any neurological or psychiatric condition either during their careers or during

retirement." Either this assertion by Dr. Randolph was an unintentionally erroneous statement, this assertion was an intentional false statement, or Dr. Randolph has on more than one occasion knowingly co-authored a paper that presented scientific data that he considers to not be "credible." Regardless, this incongruity negates the need to further refute this assertion by Dr. Randolph.

In paragraphs 21 and 22, Dr. Randolph claims that because there is currently no effective treatment for "CTE nor any of the other neurodegenerative diseases cited by plaintiffs' experts…" a "medical monitoring program for retired NHL players would not provide any benefit above and beyond routine medical care." (Randolph ¶¶ 21-22). This demonstrates an incredibly cynical viewpoint as well as a rather biased opinion. "Routine medical care" varies widely for retired NHL athletes as well as the general public. A well-designed monitoring program would provide retired NHL athletes with access to consistently competent and appropriate medical screening and subsequent recommendations for care in the event of diagnoses. Although there may be no current treatment for many of the neurodegenerative diseases cited there are multiple publications endorsing the benefit of early diagnosis of such diseases, as well as management of such diseases by appropriate specialists such as neuropsychologists and the need for additional research to further evaluate the benefits of early diagnosis. For example, a recent publication reporting results of a literature review of benefits and challenges of earlier diagnosis of Alzheimer's (Dubois B, Padovani A, Scheltens P, Rossi A, and Dell'Agnello G. Timely Diagnosis for Alzheimer's

Disease: A Literature Review on Benefits and Challenges. J Alzheimers Dis. 2016;49(3):617-31.) concluded, "Timely diagnosis at the prodromal stage of the disease could offer many potential benefits to patients and caregivers, especially the opportunity to obtain treatment to control symptoms, avoid medications that may worsen symptoms, and, possibly in the future, access to interventions that slow or lessen the disease process. Patients could put into place advance care planning and make end-of-life decisions, consider changing unhealthy lifestyles, and seek better medical care."

One really doesn't need a pile of research papers to intuitively grasp the importance of providing early diagnosis of dementia, or other long term negative health effects of sports-related concussion, to retired NHL players and their families to enable them to make the most informed decisions about their immediate and long-term plans for healthcare as well as more general life planning. To withhold information that would allow an individual to make these intensely personal decisions is unethical.

Additionally, the authors did acknowledge their findings were mainly based on expert opinion and that "further studies are needed to demonstrate not only that a timely diagnosis is feasible, but also that it has benefits." Establishing a medical monitoring program for retired NHL players would not only enable these individuals to make informed planning decisions for themselves and their families, but would also provide the opportunity to conduct exactly the type of studies that will be required to quantify the potential benefits of early diagnosis and

management. This very intentional attempt by Dr. Randolph, as well as other defendants' experts, to first claim sufficient evidence does not exist to support plaintiffs' assertions, but then to turn around and claim the exact studies that *would* satisfy their unreasonably high standards for proving causation should not be conducted is counter to basic scientific practice and, in this case, quite self-serving. If only a prospective longitudinal cohort study of retired NHL players can suffice to either prove or disprove the proffered causal association between playing in the NHL, sustaining sports-related concussion(s), and subsequent long term negative health effects, then why are defendants' experts so adamantly opposed to someone conducting exactly such a study?

At paragraph 23, Dr. Randolph asserts that the epidemiologic studies proposed are methodologically flawed. This is an inappropriate conclusion given the format of my proposal. I was asked to provide a brief (i.e., 1 to 2 page) proposal of potential study designs. An interpretation of the methodological strengths and weaknesses of such a brief proposal is inappropriate. If afforded the opportunity to submit a full study proposal similar to an NIH RO1 proposal (i.e., 10 pages for the research strategy with an additional page for just the specific aims) it would be very easy to address Dr. Randolph's concerns regarding the methodological strengths and weaknesses of the proposed studies.

For example, while Dr. Randolph is correct in contending that studies relying upon voluntary participation may suffer from ascertainment bias because players who agree to participate may differ from those who do not in ways

important to the testing of the study hypotheses, he failed to note two important features of longitudinal studies of occupational populations of interest (in this case retired NHL players): 1) because it is unethical to make study participation mandatory for retired workers the potential for ascertainment bias is a well-known and well-tolerated feature of all studies of retired workers across occupational settings and 2) because this is an unavoidable bias there are multiple means of limiting this bias including enrolling a large sample size representing a significant proportion of the population of interest, enrolling a representative sample, offering a large incentive to encourage participation, engaging unions to endorse the study to encourage participation, engaging clinicians caring for the retirees to endorse the study, conducting multiple studies simultaneously to capture a broader sample of retirees (for example, in this case a study of long term negative health effects of head injury could be concurrently run with a study of early onset osteoarthritis from knee injuries) etc.

Further, the contention that my proposed study was flawed due to lack of a control group is merely a function of the brevity of the proposal outline. I agree that obtaining control data is important. However, Dr. Randolph appears to insinuate that the only way to provide controls for a study of retired NHL players would be to enroll "a sample of men demographically matched to NHL retirees with no history of extensive involvement in contact sports." This is ironic given his above concern since the same also applies to controls (i.e., members of the general population with no history of contact sports involvement who are willing

to participate in a prospective longitudinal study may differ from individuals unwilling to participate in important ways). Additionally, there are multiple means of addressing this concern including: 1) using existing population based prevalence data captured in other studies as a control comparison group, 2) using uninjured controls from the same population (i.e., enrolling a matched control NHL player who had never sustained a serious injury, 3) using "injured controls" from the same study population (i.e., enrolling a matched control NHL player who had never sustained a concussion but who had sustained another serious injury such as a knee ligament injury), etc. If allowed the opportunity to present a full study proposal I am quite confident Dr. Randolph's concerns would be adequately addressed.

Additionally, Dr. Randolph's contention that the merits of such a study should be "adjudicated" by the NIH demonstrates his lack of experience conducting the type of multi-decade prospective cohort study of a sports-related injury that would be required here. In general NIH supports basic research (e.g., bench science, improvements to diagnostic imaging, efforts to identify biomarkers, etc.), but it has largely failed to support (at least in recent decades) extended prospective cohort studies of sports-related health issues. In fact, the UNC study of retired NFL players was initially funded by the NFL and subsequently has largely continued to be funded by the NFL and other NGOs rather than federal entities such as the NIH. Dr. Randolph's failure to recognize the incredibly low likelihood that any study of retired NHL athletes, regardless of the strength of the

study methodology, indicates he may not be qualified to evaluate the methodological strength of the proposed studies – in either the provided brief format or a full 11 page format. Just as Dr. Randolph contends that study proposals "should have their scientific merits adjudicated by an appropriate mechanism (e.g., NIH grant review), rather than by the courts…" I contend this brief study proposal should have its scientific merits adjudicated by grant review boards of potential funding agencies rather than by his Declaration.

2. *Responses to Randolph's Discussion Section*

In paragraph 25 (a) Dr. Randolph claims that it is not even necessary to consider second impact syndrome "…because retired NHL players are obviously at no greater risk of incurring concussions (or closely spaced concussions) than other men their age in the general population." (Randolph ¶25(a)). This is not an accurate statement. It may or may not be fair to state that retired NHL players who had never been diagnosed with a concussion are at no greater risk than the general population of incurring concussions. However, there is an impressive body of literature concluding that concussion history is a risk factor for subsequent concussion and delayed recovery following subsequent concussion. For example, Dr. Randolph himself was a co-author of a paper that concluded, "Our study suggests that players with a history of previous concussions are more likely to have future concussive injuries than those with no history…and previous concussions may be associated with slower recovery of neurological function." (Guskiewicz KM, McCrea M, Marshall SW, Cantu RC, Randolph C, Barr W,

Onate JA, and Kelly JP. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. JAMA. 2003;290(19):2549-55.).

Just because most of these papers have looked at concussion history as a risk factor for a subsequent sports-related concussion does not mean that NHL players' risk for subsequent concussion disappears immediately upon their retirement. An example may be found in a more recent study of US Army soldiers found that pre-deployment TBI history was a predictor of sustaining a deployment mTBI with subsequent persistent post-concussive symptoms (Stein MB, Urasano RJ, Campbell-Sillis L, Colpe LJ, Fullerton CS, Heeringa SG, Nock MK, Sampson NA, Schoenbaum M, Sun X, Jain S, and Kessler RC. Prognostic indicators of persistent post-concussive symptoms after deployment-related mild traumatic brain injury: a prospective longitudinal study in U.S. Army soldiers. J. Neurotrauma. 2016;33(23):2125-2132.). Pre-deployment history of mTBI may have been from numerous activities (e.g., car crashes, falls, occupational injuries, interpersonal violence), but it was very unlikely to have been due to the types of activities associated with deployment (e.g., blast injuries, firearm injuries, etc.) and yet those pre-deployment mTBI increased the soldiers risk of deployment mTBI. Thus, it is logical to infer that if an athlete with a history of concussion has an increased risk of sustaining a subsequent sports-related concussion then he is also at increased risk of sustaining a concussion from other activities (e.g., car crashes, falls, occupational injuries, interpersonal violence, etc.) that can result

from similar mechanisms (i.e., direct blows to the head or blows to the body that result in accelerative and rotational forces of the brain within the skull). Even if Dr. Randolph is unwilling to follow this logical line of inference he must admit there is no evidence in the peer-reviewed literature to support *his* claims that "retired NHL players are obviously at no greater risk of incurring concussions (or closely spaced concussions) than other men their age in the general population" since the type of decades long prospective cohort study of the health of retired NHL players required to make such a conclusion have not yet been conducted. Frankly, this need to accurately determine the relative risk of concussion among retired NHL players compared to men their age in the general population is yet another reason why a medical monitoring program for retired NHL players is needed.

In paragraph 25 (b) Dr. Randolph boldly claims that prospective studies have conclusively demonstrated that recovery from concussion is extremely rapid and complete. Again, this is simply not true. To state that all concussed individuals recover fully even within a few days ignores a very large number of peer-reviewed publications that provide clear evidence not just that some concussed athletes take longer than a few days to recover, but which actually provide the proportion and/or rate of athletes studied who take substantially longer to recover. This body of literature includes multiple publications reporting on collegiate and high school athletes, although such delayed recovery is not usually clinically diagnosed as PCS in those studies. Additionally, the above referenced

prospective longitudinal study of U.S. Army soldiers (Stein et al, J Neurotrauma. 2016;33(23):2125-2132.) proves the point. That study followed a cohort of 4,518 soldiers from 1-2 months before a 10-month deployment to Afghanistan on to redeployment to the United States and subsequent evaluations approximately 3 months and 9 months post return to the US. The authors specifically utilized presence and severity of post-concussive symptoms as the outcome of interest, finding that after adjusting for demographic, clinical, and deployment-related factors, deployment-acquired mTBI was associated with *nearly triple the risk* of reporting any PCS and with increased severity of PCS when symptoms were present. Taken together, the large number of publications reporting athletes with symptoms persisting beyond "a few days" and the prospective controlled study of soldiers that demonstrated PCS existed at 3 and 9 months post return to US (note, this is not post injury but post return which means PCS time post injury was even longer) clearly contradict Dr. Randolph's claim that all concussed athletes recover quickly and none of them have PCS. It is quite shocking to read such a claim which is not only unsubstantiated but, frankly, directly in contrast with the accepted body of knowledge.

In paragraph 25 (c) (iv) Dr. Randolph claims there is no evidence of any increased risk of any type of neurological or psychiatric disease in retired NHL players or any players of any contact sport and he further asserts that NFL retirees are much healthier physically and mentally than men of their age in the general population. Once again, this is simply false and ignores a substantial body of

published literature indicating there are serious health concerns among retired professional contact sport athletes. To provide just one of the many examples, a 2012 cohort study of depression among retired professional football players concluded "Professional football players self-reporting concussions are at greater risk for having depressive episodes later in life compared with those retired players self-reporting no concussions" (Kerr ZY, Marshall SW, Harding HP, and Guskiewicz KM. Nine-year risk of depression diagnosis increases with increasing self-reported concussions in retired professional football players. Am J Sports Med. 2012;40(10):2206-12.).

While there have been other publications that have found no statistically significant increased risk of specific long term negative health effects among retired professional contact sports athletes, there are other newer publications that continue to demonstrate concerning findings. For example, a 2016 publication reported "A disproportionate number of completed suicides in current and former professional football players have occurred since 2009 (42.3%)" (Webner D and Iverson G. Suicide in professional American football players in the past 95 years. Brain Inj. 2016;30(13-14):1718-1721.). Thus, it is simply false to assert, as Dr. Randolph has, that there is no known evidence of any increased risk of any type of neurological or psychiatric disease in retired players of any contact sport.

In fact, even if one restricts the analysis of the literature to a strong systematic review using the very stringent and restrictive criteria of another of defendants' experts (Cassidy), a recently published systematic review of potential

long-term effects of sport-related concussion can be found in which a group of researchers, that included Dr. Randolph, followed Dr. Cassidy's criteria for a strong systematic review by ensuring: 1) the study reviewed papers from multiple databases – even engaging a health sciences librarian using the CADTH Peer Review Checkist for Search Strategies, 2) the study had strict study selection criteria described using a PRISMA diagram, and 3) the study assessed risk of bias and level of evidence using the Downs and Black checklist. (Manley G, Gardner AJ, Schneider KJ, Guskiewicz KM, Bailes J, Cantu RC, Castellani RJ, Turner M, Jordan BD, Randolph C, Dvorak J, Hayden KA, Tator CH, McCrory P, and Iverson GL. A systematic review of potential long-term effects of sport-related concussion. Br J Sports Med. 2017;51(12):969-977.)

That strong systematic review of 3,819 studies, of which 47 met the inclusion criteria, found "Some former athletes have depression and cognitive deficits later in life, and there is an association between these deficits and multiple prior concussions." and "Some retired professional American football players may be at increased risk for diminishment in cognitive functioning or mild cognitive impairment (several studies), and neurodegenerative diseases (one study)."

Similarly, another recently published systematic review concluded, "There is strong evidence that a history of concussion in American football players is associated with depression later in life and short-term physical dysfunctions." (Vos BC, Nieuwenhuijsen K, and Sluiter JK. Consequences of traumatic brain injury in professional American football players: a systematic review of the

literature. Clin J Sport Med. 2017;May 9:doi 10.1097 epub ahead of print.) Thus, even when the vast majority of the published literature is ignored in order to meet the unreasonably restrictive requirements of Dr. Cassidy, there is still ample evidence that athletes who have experienced a concussion are at increased risk of long term negative health effects.

In paragraph 25 (d) (ii) Dr. Randolph states his personal opinion that it is impossible to make any conclusions regarding causal associations between playing sports and white matter loss until several long-term, longitudinal, controlled, prospective studies have been completed. This is simply a reiteration of the false conception of causality endorsed by Dr. Cassidy. This incredibly narrow view ignores the valued and long supported epidemiologic approach of considering the entire body of knowledge and evaluating whether a preponderance of evidence of causation exists (utilizing guidelines such as Hill's Criteria for Causality). Please see my rebuttal to Cassidy Declaration (above) for a full response to Drs. Randolph's and Cassidy's inappropriate interpretation of assessment of causality.

In paragraph 26 Dr. Randolph asserts that medical monitoring programs are only beneficial for individuals with known risk for a particular disease for which there is treatment which can alter the outcome from the disease with early intervention. This is simply unfounded. There are numerous examples of medical monitoring of populations of interest for multiple reasons. For example, health care workers are routinely monitored for signs of TB infection as a means of protecting patients, and licensed sex workers are routinely monitored for signs of

STDs as a means of protecting their clients. Additionally, many populations with untreatable diseases are medically monitored as a way to provide improved management of symptoms, to conduct research studies that could lead to future treatments, and as a way of providing the individuals and their families with knowledge of their disease's average life course to enable them to make informed decisions regarding quality of life and medical care issues as their disease progresses.

Additionally, as outlined above (in response to Randolph's assertions in paragraphs 21 and 22) it is quite arrogant to claim that retired NHL players could not benefit from a well-designed medical monitoring program when there is evidence that such monitoring, which can lead to early diagnosis of negative health outcomes, can at a minimum provide retired athletes and their families with knowledge that will enable them to make informed decisions regarding quality of life and health care issues. Additionally, as mentioned above, a well-designed medical monitoring system would provide the opportunity to conduct the very studies (i.e., decades long prospective longitudinal cohort studies) the defendants' experts claim are required before they will consider making any conclusions regarding causality. There is no reason to provide a point by point response to the sub-points of point 26 because the introductory statement is so deeply flawed.

In paragraph 27 Dr. Randolph finds two flaws with my proposed studies, ascertainment bias and lack of a control. But, as explained above, Dr. Randolph's criticism of the proposed epidemiologic studies is not appropriate since only a

very brief 1 page abstract of each of the two study proposals was provided in my Declaration. All of Dr. Randolph's critiques are easily addressed if, at some future date, I or other sports-injury epidemiologists are afforded the opportunity to submit a full study proposal similar to an NIH RO1 proposal (i.e., 10 pages for the research strategy with an additional page for just the specific aims) which will allow for full discussion of proposed study methodology strengths and weaknesses.

Finally, with regard to some of Dr. Randolph's own research it is interesting that some of his more recent research has been in the areas of measuring cognitive decline and "Recommended cognitive outcomes" in preclinical Alzheimer's disease (Refs #81, 82, and 83). Given his assertion in his Summary of Opinions at paragraphs 21 and 22, that none of the neurodegenerative diseases of interest in this case (e.g., Alzheimer's, ALS, etc.) are curable and therefor a medical monitoring program for retired NHL players would not provide any benefit, then why is Dr. Randolph performing this research? If one were to apply Dr. Randolph's own logic, his research in pre-clinical Alzheimer's disease should not be warranted until *after* a cure capable of altering the disease course is found. If, as one could rather infer based on this research, Dr. Randolph does believe there is some benefit in early monitoring of/testing of pre-clinical Alzheimer's disease then why would there not also be some benefit to early monitoring of/testing of retired NHL players?

Conclusion of Randolph Rebuttal

I am concerned that Dr. Randolph has made so many untrue assertions based on his review of the literature (e.g., "There are no credible scientific data suggesting that retired athletes from any contact sport, including hockey, are at increased risk for any neurological or psychiatric condition either during their careers or during retirement" and a "medical monitoring program for retired NHL players would not provide any benefit above and beyond routine medical care."), particularly when his own co-authored work contradict his assertions. Regardless, the root difference between our two reviews and our conclusions regarding the current state of knowledge is that I am convinced that a sufficient body of knowledge exists to state that NHL players are at increased risk of concussion and that NHL players who sustain concussions are at increased risk of negative long term health effects. I am convinced that a well-designed medical monitoring program will serve both to help current retired NHL players (e.g., earlier diagnosis, better access to care, additional knowledge upon which to make quality of life and medical care decisions) and also to provide opportunities to conduct the very type of research that could one day drive treatments as well as more effective prevention efforts. Dr. Randolph, on the other hand, falsely claims there is no literature demonstrating any concerns regarding the brain health of contact sport players, including hockey players and that a medical monitoring program for retired NHL players will provide no benefit to current or future retired players.

C. Point by Point Response to Declaration of Lisa Brenner

1. Observations about Dr. Brenner's background and sources

Although Dr. Brenner is a well-respected clinician her background is predominantly in active duty and VA populations. This raises an interesting dilemma for the NHL who must concede either: 1) it is appropriate to review studies reporting results of non NHL players and particularly pertinent to discuss results from studies of NFL players since the mechanisms of injury, epidemiology of injury, and likely long term effects of a checking related injury in the NHL is undoubtedly more similar to a tackle related injury in the NFL than it is to a blast related injury sustained by an active duty service member or 2) Dr. Brenner is not qualified to serve as an expert witness on this case given her expertise lies in concussions and TBI in active duty and VA populations and she has done very little work in sports related concussions.

For example, on page 2 of her declaration Dr. Brenner states her research has focused on TBI and co-occurring psychiatric conditions. This indicates she believes there are co-occurring psychiatric conditions associated with TBI. This is something denied by defendant's experts Drs. Cassidy and Randolph.

Again on page 3 Dr. Brenner states that she is conducting research related to TBI and co-morbid psychiatric disorders and negative outcomes including suicide. Again, if Dr. Brenner did not believe there was a potential causal association between TBI (regardless of whether that is with or without concurrent

co-morbid psychiatric disorders) and negative outcomes including suicide she would not be conducting such research. For instance, if she truly believed the increased risk of suicide was solely attributed to the psychiatric disorders, regardless of TBI, then there would be no need for her to be studying TBI and co-morbid psychiatric disorders. This clearly indicates Dr. Brenner believes that TBI at a minimum plays a role in the association between psychiatric disorders and negative outcomes including suicide. This is something denied by defendant's experts Drs. Cassidy and Randolph.

2. *Rebuttal to Dr. Brenner's Summary of Opinions.*

Similar to my rebuttal of Drs. Cassidy and Randolph's declarations I disagree with Dr. Brenner regarding her interpretation of the quality of the studies making up the current body of knowledge and her assertion that there is an inability to infer causality based on a preponderance of evidence supported by hypothesis-generating studies. Similarly I believe it is no longer appropriate to assert that the established and still growing body of work reporting associations between repetitive mTBIs and long term negative health outcomes "remains preliminary" – as supported by the many citations I have provided in my rebuttals to Drs. Cassidy and Randolph.

Additionally, it is not entirely appropriate for Dr. Brenner to conflate evidence-driven changes to clinical practice (i.e., the individual decision making of individual clinicians regarding the care of individual patients) and "clinical best practices" (i.e., the guidelines for clinical care developed by and distributed to

specific professional groupings of clinicians, often through position statements). While it may very well be more appropriate, in theory, to cite Grant Iverson's work when referring to how professional clinical groups' position statements regarding concussion diagnosis and management should be developed, it is not nearly as applicable for individual clinician's practices which may largely be based on their own review and interpretation of the published literature.

Regardless, it is disingenuous to insinuate that Iverson's conclusion that there is usually a lag time of 17 years between publication of research findings and their translation into clinical practice in the case of sports-related concussions where (as acknowledged by Dr. Brenner in her Figure 4) there has been a dramatic increase in the amount of concussion research published in the peer-review literature over the past decade which has directly coincided with dramatic and rapid changes in clinical diagnosis and management of concussions (e.g., rapid development of new diagnostic tools and criteria, changes in interpretation of concussion severity from old scaling criteria based largely on LOC to new interpretations based heavily on length of time to full symptom resolution, changes in management of concussed athletes from allowing them to return to play immediately to graduated return to play guidelines incorporating increasing levels of physical activity, to a brief foray by some clinicians to "cocoon therapy" devoid of any physical activity, to an accelerated graduated return to play guideline for professional athletes, etc.). Simply stated, clinical practices quickly adopted new processes surrounding diagnosis and treatment of concussions over the past 15

years despite Drs. Cassidy, Randolph, and Brenner's assertions that there does not yet exist conclusive evidence regarding concussion and either short or long term negative health outcomes. Additionally, a multitude of professional clinical organizations have released position statements on diagnosis and management of concussion (i.e., statements of clinical best practices) which are not actually based on the types of research studies (e.g., prospective longitudinal cohort studies) claimed by Drs. Cassidy, Randolph, and Brenner to be required to make conclusive decisions regarding either causation or clinical care practices.

3. *Responses to Dr. Brenner's Literature Review*

Throughout this section Dr. Brenner provides a basic primer on evidence-based clinical decision making to support her primary assertion that large classes of study methodologies (case reports/series, cross-sectional studies, case-control studies, etc.), those she inappropriately restricts as only being capable of hypothesis-generating (which I discuss above in response to Dr. Cassidy's declaration) are not sufficient to establish "rigorous evidence-based practices." While this may or may not be the hypothetical gold standard by which clinical care should be guided, it simply is not how medicine is currently practiced in the US.

This can be demonstrated by outlining how clinical practices have evolved in the area of concussion diagnosis and care over the past decade or so despite the lack of Dr. Brenner's level of hypothesis-testing studies providing results driving

"rigorous evidence-based practices." There are three important points to this illustration:

First, over the past 15 years numerous professional clinical organizations released position statements/guidelines (or updates to prior position statements/guidelines) on concussion which included their recommended best practices for their clinical specialty regarding concussion diagnosis and/or management. It is important to note that, despite Dr. Brenner's claim that such "clinical best practices" are borne only from systematic review of hypothesis generating studies that meet her definition of being able to drive evidence-based practice, this simply has not been the case in these concussion statements. For example, to update of their 1997 practice parameters, the American Academy of Neurology (AAN) reported that they commissioned a systematic review of the literature from 1955 to June 2012 which "assessed evidence for quality and synthesized into conclusions using a modified Grading of Recommendations Assessment, Development and Evaluation process." using a modified Delphi process to develop recommendations (Giza C, Kutcher JS, Ashwai S, Barth J, Getchius TS, Gioia GA, Gronseth GS, Guskiewicz K, Mandel S, Manley G, McKeag DB, Thurman DJ, and Zafonte R. Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;80(24):2250-7.). Despite Dr. Brenner's assertions regarding requirements for policy statements, they reported, with respect to "what

interventions enhance recovery, reduce the risk of recurrent concussion, or diminish long-term sequelae," they concluded "Each of several studies addressed a different aspect of postconcussion intervention, providing evidence that was graded as very low to low" and "On the basis of the available evidence, no conclusions can be drawn regarding the effect of postconcussive activity level on the recovery from SRC or the likelihood of developing chronic postconcussion complications." Yet, in the practice recommendations that followed, the authors included a section "RTP: Graded physical activity" in which they advised "LHCPs might develop individualized graded plans for return to physical and cognitive activity, guided by a carefully monitored, clinically based approach to minimize exacerbation of early postconcussive impairments (Level C)." This is just one example of a professional clinical organization providing recommendations for clinical care despite a self-proclaimed lack of strong evidence to support those recommendations. Clearly, Dr. Brenner's hypothesized gold standard is not rigidly endorsed in the real world of clinical care.

As another example, the majority of professional clinical organizations have, beginning from around 2001, largely endorsed a medically supervised multistep return to play protocol for managing concussed athletes which follows the protocol provided in the first International Conference on Concussion in Sport held in Vienna in 2001 (Aubry M, Cantu R, Dvorak J, Graf-Baumann T, Johnston K, Kelly J, Lovell M, McCrory P, Meeuwisse W, and Schamasch P. Summary and agreement statement of the first International Conference on Concussion in

Sport, Vienna 2001. Br J Sports Med. 2002;36(1):6-10.) and which has changed little through the multiple subsequent international conferences culminating in the 5th International Conference on Concussion in Sport which was held in Berlin in 2016 (McCrory P, et. al. Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med. 2017;April 26: doi: 10.1136 e-pub ahead of print). There has been widespread clinical adoption of this medically supervised, multistep return to play protocol despite the fact that these international consensus statements have never provided any citation to any prospective longitudinal cohort study demonstrating the effectiveness of this concussion management strategy. In fact, the manuscript reporting the consensus statement resulting from the 5th International Conference states "Most consensus and agreement statements for managing SRC recommend that athletes rest until they become symptom-free. Accordingly, prescribed rest is one of the most widely used interventions in this population.

The basis for recommending physical and cognitive rest is that rest may ease discomfort during the acute recovery period by mitigating post-concussion symptoms and/or that rest may promote recovery by minimizing brain energy demands following concussion." However, there are no citations provided to support those assertions. Further, the statement goes on in the following paragraph to note "There is currently insufficient evidence that prescribing complete rest achieves these objectives" and "It is reasonable for athletes to avoid vigorous exertion while they are recovering. The exact amount and duration of

rest is not yet well defined in the literature and requires further study." The widespread adoption of graduated return to play policies as clinical best practice by multiple professional clinical organization despite a lack of any supporting studies meeting the standards set by Drs. Brenner, Cassidy, and Randolph for studies capable of driving causal inferences and evidence-based clinical practices clearly demonstrates that these assertions are simply that, their personal assertions, and do not reflect actual clinical practice regarding concussion management.

Second, even when multiple cohort studies do exist, clinicians can continue to be in wide disagreement regarding how, or whether, the findings of such studies should drive clinical practices. A pertinent example is the fact that the robust body of literature on computerized neurocognitive testing (CNTs) has not driven uniform clinical practices regarding the use of CNTs in concussion diagnosis and management. It is actually quite interesting to follow the history of CNTs in the peer-reviewed literature. For example, at the same time that proponents of CNTs were publishing validity studies (Iverson GL, Lovell MR, Collins MW. Validity of ImPACT for measuring processing speed following sports-related concussions. J Clin Exp Neuropsychol. 2005;27(6):683-9.), opponents of their use were reporting that although CNTs were being commercially marketed to professional, collegiate, high school, and elementary school programs as a way of detecting the effects of sport-related concussion in order to aid in RTP decisions there were no studies supporting such clinical use of CNTs (*See e.g.* Randolph C, McCrea M, Barr WB. Is neuropsychological testing useful in the management of sport-related

concussion? J Athl Train. 2005;40(3):139-52) which includes the statement, "Despite the theoretic rationale for the use of NP testing in the management of sport-related concussion, no NP tests have met the necessary criteria to support a clinical application at this time."

Despite concerns regarding reliability of CNTs it was acknowledged that "Computer-based neurocognitive assessment programs commonly are used to assist in concussion diagnosis and management. These tests have been adopted readily by many clinicians based on existing test-retest reliability data provided by test developers." (Brogllio SP, Ferrara MS, Macciocchi SN, Baumgartner TA, Elliott R. Test-retest reliability of computerized concussion assessment programs. J Athl Train. 2007;42(4):509-14.). However, even as these CNTs were widely adopted by clinicians some raised concerns regarding which clinician specialties were and were not adequately trained to utilize CNTs in the care of concussed athletes (Echemendia RJ, Herring S, Bailes J. Who should conduct and interpret the neuropsychological assessment in sports-related concussion? Br J Sports Med. 2009;43(Suppl 1):132-5.). Despite the continued questions over the reliability and clinical utility of CNTs (Nelson LD, LaRoche AA, Pfaller AY, Lemer EB, Hammeke TA, Randolph C, Barr WB, Guskiewica K, and McCrea MA. Prospective, head-to-head study of three computerized neurocognitive assessment tools (CNTs): reliability and validity for the assessment of sport-related concussion. J Int Neuropsychol Soc. 2016;22(1):24-37) it is widely acknowledged that neuropsychological assessment has become a key component

of evaluation of concussed athletes. Subsequently, over the past 2 decades a number of CNTs have been developed for the assessment of sports-related concussion, such that "Standardized neurocognitive assessment tools are now commonly used across the continuum of concussion care, ranging from the sports sideline to critical care setting and the outpatient concussion clinic" (McCrea MA, Asken B, and Nelson LD. Neurol Clin. 2017;35(5):487-500.). This is another clear example of how clinical practice regarding concussion diagnosis and management across a wide range of clinical specialties evolved over the past decade not due to strong evidence-based knowledge as Dr. Brenner claims must always occur, but actually happened despite ongoing concerns regarding the reliability and validity of CNTs, the actual clinical utility of CNTs, and which clinical specialties are qualified to assess CNTs. Thus, Dr. Brenner's assertions regarding the progression of clinical decision making simply does not reflect the reality of clinical decision making with respect to sports related concussion diagnosis and management.

Third, clinicians in the United States strongly believe that they alone are best capable of providing care for their patients as evidenced in their acceptance of the appropriateness of off-label prescribing which is described by the US Department of Health & Human Services Agency for Healthcare Research and Quality (AHRQ) as "when a physician gives you a drug that the U.S. Food and Drug Administration [FDA] has approved to treat a condition different than your condition." Off-label prescribing quite literally means that physicians feel it is

appropriate to prescribe medications to their patients which have not yet reached the level of appropriate evidence-based care as determined by the FDA. Despite Dr. Brenner's assertions that clinical care should *always* rely upon rigorous evidence-based practices, off label prescribing is often both legal and common in the United States. According to AHRQ, "In fact, one in five prescriptions written today are for off-label use." Perhaps this pervasive perception fed into defendant's expert's assertion that only an athlete's physician should decide what information from the peer-reviewed literature should, and should not, be shared with a concussed athlete.

Conclusion of Brenner Rebuttal

Dr. Brenner's idealistic view regarding how clinical practice and consensus clinical guidelines should evolve simply does not reflect the reality of how clinical practice regarding concussion diagnosis and management has evolved, particularly over the past 15 years.

R. Dawn Comstock

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 7th day of Feb, 2017